(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 527 936 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
23.07.1997 Bulletin 1997/30

(21) Application number: 91910470.3

(22) Date of filing: 06.05.1991

(51) Int. Cl.[6]: A61F 2/44

(86) International application number:
PCT/US91/03106

(87) International publication number:
WO 91/16867 (14.11.1991 Gazette 1991/26)

(54) PROSTHETIC INTERVERTEBRAL DISC

BANDSCHEIBENPROTHESE

DISQUE INTERVETEBRAL PROTHETIQUE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: 07.05.1990 US 520027

(43) Date of publication of application:
24.02.1993 Bulletin 1993/08

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Printed by Rank Xerox (UK) Business Services
2.14.11/3.4

Serial No. 10/812,268
Ref. B24

Description

BACKGROUND OF THE DISCLOSURE

The present invention is in the field of implantable medical devices, and more particularly, is directed to devices useful as a prosthetic intervertebral disc.

The intervertebral disc acts in the spine as a crucial stabilizer, and as a mechanism for force distribution between the vertebral bodies. Without the disc, collapse of the intervertebral space occurs in conjunction with abnormal joint mechanics and premature development of arthritic changes.

Prior art methods of treating injured or diseased discs have included chemical disintegration procedures and surgical excision, often followed by bony fusion to prevent spinal collapse or instability. With excision, no significant regeneration of vertebral tissue occurs. Replacement of an injured disc in an otherwise healthy spine may prevent arthritic changes and may stabilize the spinal segments. In diseased spines, replacement of the disc may reduce the progression of the disease process, and may provide pain relief.

In alternative prior art replacement approaches, discs have been replaced with prostheses composed of artificial materials. The use of purely artificial materials in the spine minimizes the possibility of an immunological response. In addition, such materials permit construction of a structure which can withstand the high and repeated loads seen by the spinal vertebral joints, and can alter the joint mechanics in beneficial ways that biological materials would not tolerate. For example, titanium, (Albrektsson et al. (1981) Acta Ortop. Scan. 52:155-170), acrylic (Cleveland (1955) Marquette Med. Rev. 20:62; Hamby et al.(1959) J. Neurosurg. 16:311), polytetrafluorothylene-carbon fiber (Alitalo (1979) Acta Veterinaria Scandinavica Suppl. 71:1-58), and steel discs (Fenstrom (1973) Acta Chir. Scand. 4:165-186; French Patent No. 4,349,921) have been used to replace the resected disc. Each of these efforts have met with failure due to continued collapse of the disc space or erosion of the metal prosthesis into the surrounding bone.

A prosthetic intervertebral disc has also been constructed from resilient materials such as silicone rubber (e.g., Edeland (1985) J. Biomed Eng. 7:57-62; Schneider et al. (1974) Z. Orthop. 112:1078-1086; Urbaniak et al. (1973) J. Biomed. Mater. Res. Symposium 4:165-186). A disc has also been made from resilient plastic materials to form a bladder as disclosed in U.S. Patent Nos. 3,875,595 and 4,772,287; however, failure to restore full stability and normal joint biomechanics has prevented success. Porous elastomeric materials as described in U.S. Patent No. 4,349,921 have failure to recapitulate the normal vertebral body mechanics.

Generally, the replacement of intervertebral tissue with structures consisting of artificial materials has been unsuccessful principally because the opposing vertebral end plates of human and animal joints are fragile. The end plates in the spine will not withstand abrasive interfaces nor variances from normal compliance, which evidently result from the implantation of prior art artificial discs. Additionally, joint forces are multiples of body weight which, in the case of the spine, are typically over a million cycles per year. Thus far, prior art artificial discs have not been soft or durable enough, nor have they been able to be positioned securely enough to withstand such routine forces.

Prostheses, in general, have been devised out of at least some of the constituents of the structures which they are replacing, or out of materials not considered to be immunogenic to the body. For example, Yannas et al. fashioned blood vessel grafts (U.S. Patent No. 4,350,629), synthetic epidermis (U.S. Patent No. 4,448,718), and sciatic nerve guides (WO 89/10728; Yannas (1979) Am. Chem. Soc. 16:209) out of collagen and glycosaminoglycans, biochemical components of many body organs. By adjusting the pore size and axes of the pores and fibers comprising these structures, regrowth of natural tissue could be stimulated. Further regrowth has been advanced by seeding of the nerve guide with Schwann cells prior to implantation (see U.S. Patent No. 4,458,678). However, even with the foregoing technologies which have been applied to the reconstruction of anatomical structures other than intervertebral discs, a structure suitable as a prosthetic disc and constructed from natural materials has not yet been successfully developed.

Accordingly, it is an object of this invention to provide an intervertebral disc replacement or prosthesis.

Another object is to provide an improved disc replacement or prosthesis that does not interfere with normal vertebral segment motion as such interference could lead to a reduced range of motion or to focal concentration of force at other sites within the spinal column or instability of the opposing vertebral bodies, therefore enhancing the chances of progressive arthritic destruction.

Yet another object is to provide an improved disc replacement or prosthesis that is biomechanically able to withstand normal spinal column forces and is able to function at those loads to protect the opposing end plates and stabilize the joints.

The invention has aimed to provide an improved disc replacement or prosthesis which promotes regrowth of intervertebral disc material and which acts as a scaffold for fibrocartilage infiltration, and which does not evoke an immunologic reaction or aggravate other joint structures.

Prior art from which the invention commences comprises WO-A-8900413 and FR-A-2124815. WO-A-8900413 discloses a prosthetic meniscus, i.e. it is a prosthetic device for implanting in the knee. FR-A-2124815 discloses a prosthetic intervertebral disc made of materials "compible" with the body chemistry. As explained in FR-A-2124815 "compatible" means, inter alia, that the materials are resistant to attack by body fluids.

The present invention is as defined in the claims; claim 1 which is directed at a prosthetic intervertebral disc commences from FR-A-2124815.

SUMMARY OF THE INVENTION

The present invention provides a biocompatable and bioresorbable structure for implantation into the spine which assumes the form and role of an intervertebral disc. This matrix may promote regrowth of intervertebral fibrochondrocytes and provides a scaffold for the regenerating intervertebral disc tissue.

The prosthetic disc is composed or a dry, porous, volume matrix of biocompatable and bioresorbable fibers. The matrix is adapted to have in vivo an outer surface contour substantially the same as that of a natural intervertebral disc. A portion of the fibers may be cross-linked.

The fibers include a natural fiber or an analog of a natural fiber such as a biosynthetic analog, or a synthetic fiber, or mixtures thereof. A biosynthetic fiber is one which may be produced by recombinant DNA technology including the transfection of an appropriate host cell capable of protein expression with a gene encoding, for example, a recombinant protein such as collagen. A synthetic fiber is one which may be produced by chemical methods such as, automated peptide synthesis. In one preferred embodiment of the invention, the fibers of the matrix are polymers of, for example, natural molecules such as those obtained from animal or human tissue. Natural fibers useful for the same purpose preferably include collagen, elastin, reticulin, analogs thereof, and mixtures thereof.

In some forms of the invention, the fibers may be randomly orientated throughout the matrix, or may be ordered at specified regions. Alternatively, the fibers may assume substantially circumferentially extending or substantially radially extending orientations throughout the prosthetic disc.

The matrix may also include glycosaminoglycan molecules (GAGs) interspersed with the fibers. GAGs are mucopolysaccharide molecules which provide lubrication and may be included in cross-links for the prosthetic disc. In one preferred aspect of the invention, GAGs such as chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate, dermatan sulfate, heparan-sulfate, heparin, hyaluronic acid, and mixtures thereof form a component of the disc. The GAGs may be uniformly dispersed throughout the prosthetic disc as individual molecules, or may be present in varying amounts in different regions of the structure.

In various forms of the invention, GAGs may directly participate in covalent cross-linking with the fibers, or may interact with the fibers mechanically in the form of entanglement or through interlocking mechanisms, thereby forming various stable fiber-GAG complexes.

The matrix may include about 75-100% natural and/or synthetic fibers and about 0-25% GAGs by dry weight, the proportions of which may be constant throughout the structure or may be variable.

According to the invention, the matrix has a density of 0.07 to 0.50 g matrix/cm^3, where "g matrix/cm^3" is a unit connoting the number of grams in a cubic centimeter of the matrix. In addition, the matrix has an interfibrillary and intrafibrillary space of 2 to 25 cm^3/g matrix.

In another form of the invention, the prosthetic disc may further include a mesh composed of a bioresorbable, biocompatible material which is attached to lateral portions of the outer surface of the matrix. The mesh aids in the successful implantation of the prosthetic intervertebral disc into the intervertebral spaces by providing a temporary anchoring mechanism.

Implantation of a prosthetic disc according to the present invention permits regeneration intervertebral disc tissue in vivo. The presence of the prosthetic disc stimulates disc tissue growth.

Further, the invention includes a method for fabricating a prosthetic intervertebral disc of the type described above. Generally, the method includes placing a plurality of fibers or fibers and GAGs into a mold having a shape useful for spine function, subjecting the fibers (and GAGs) in the mold to two cycles of freezing and thawing, contacting the fibers or the fibers and GAGs with a chemical cross-linking reagent such that the fibers then assume the shape of the mold, and lyophilizing the resulting structure to obtain a dry, porous, volume matrix.

The fibers may be laid down in a circumferential orientation by rotating the mold as they are placed therein. Alternatively, the fibers in the mold may be compressed with a rotating piston. Radial orientation of the fibers is produced by manually painting the fibers in a linear, radially directed fashion.

Specific densities and pore sizes may be obtained in various regions of the matrix by compressing the fibers or fibers and GAGs in the mold prior to the second freeze-thaw cycle, and subsequent to the chemical cross-linking step. This may be accomplished by applying pressure to a specific region of the matrix with a piston of a predetermined shape.

In a preferred aspect of the invention, the cross-linking step is performed using chemical agents which form intramolecular and intermolecular cross-links. Useful chemical agents include, for example, glutaraldehyde, formaldehyde, biocompatible bifunctional aldehydes, carbodiimides, hexamethylene diisocyanate, bisionidates, glyoxal, polyglycerol polyglycidyl ether, glyoxal, and mixtures thereof. Particularly useful cross-linking agents are 1-ethyl, 3-(3-dimethylaminopropyl), polyglycerol polyglycidyl ether, acyl azide, and glutaraldehyde.

In other aspects of the invention, an additional cross-linking step is performed by lyophilizing the chemically cross-linked disc and then subjecting it to dehydrothermal cross-linking procedures.

The invention will next be described in connection with certain illustrated embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects of this invention, the various features thereof, as well as the invention, itself, may be more fully understood from the following description, when read together with the accompanying drawings in which:

FIG. 1 is a simplified diagrammatic representation of the normal positioning of an intervertebral disc in native position in the human spine;

FIG. 2 shows a perspective view of an exemplary prosthetic intervertebral disc in accordance with the present invention;

FIG. 3 shows a sectional view along line 3-3 of the prosthetic intervertebral disc of FIG. 2;

FIG. 4 shows a perspective view of another exemplary prosthetic intervertebral disc;

FIG. 5A shows a perspective view of another exemplary prosthetic intervertebral disc including a mesh member; and FIG. 5B shows a sectional view along line 5B-5B of the prosthetic disc of FIG 5A;

FIG. 6 shows in section an exemplary mold for constructing a prosthetic intervertebral disc; and

FIG. 7 shows in section an alternative mold for constructing a prosthetic intervertebral disc.

DESCRIPTION OF THE INVENTION

It has been discovered that a prosthetic intervertebral disc fabricated from biocompatible and bioresorbable fibers can be surgically implanted into the intervertebral space so as to provide normal joint motion and strength. This prosthetic intervertebral disc also acts as a scaffold for regenerating disc tissue whose ingrowth is encouraged by the physical characteristics of the implanted device. Following implantation, tissue ingrowth, regeneration, and finally resorption of the scaffold, natural intervertebratal tissue remains.

FIG. 1 shows the normal positioning of an intervertebral disc 100 in the human intervertebral space 110 between the vertebral bodies 120 and 130. An exemplary prosthetic intervertebral disc 200 is shown in FIG. 2. The disc 200 is a generally porous, dry volume matrix which extends circumferentially in about a central axis 10. As used herein, the term "volume matrix" refers to a porous array characterized by relatively comparable (but not necessarily equal) outer dimensions in three orthogonal directions (as contrasted with a sheet matrix which would have relatively comparable dimensions in two orthogonal directions but relatively small dimensions in a third orthogonal direction).

In the preferred form, prior to implantation, the prosthetic intervertebral disc 200 has the shape of a cylindrical pad, extending circumferentially about the axis 10, and comprising a relatively high compliance central region 12 surrounded by a relatively low compliance peripheral region 14. In FIG. 2, the separation of regions 12 and 14 is indicated generally by broken line 17, although the transition is normally gradual. In the preferred form, the top and bottom (as shown) surfaces of disc 200 are concave so that disc 200 has maximum height A at its peripheral edge of approximately 8 mm and a maximum radial dimension C of approximately 35 mm. FIG. 3 shows a sectional view along line 3-3 of the prosthetic disc 200 shown in FIG. 2.

FIG. 4 shows an additional embodiment 220 of the present invention which is similar in composition to the prosthetic disc 200 depicted in FIG. 2. The prosthetic intervertebral disc 220 is similar to disc 200, but includes convex top and bottom surfaces and further includes a mesh member 20 extending from its lateral surface. The mesh member 20 is composed of a biocompatible, bioresorbable material. Following implantation, the mesh member 20 may be sutured to adjacent tissue to anchor the disc 220 in place. The mesh member 20 may function in this capacity until sufficient tissue ingrowth occurs to provide that function. Since the anchor function of mesh member 20 is only temporary, the mesh member 20 may be a #1 mesh screen composed of absorbable suture materials such as polyglyconate, Dexon, or polydioxane (PDS) woven into a mesh. Alternatively, nonabsorbable suture materials such as expanded polytetrafluoroethylene (PTFE) may be used.

FIGs. 5A and 5B show yet another embodiment 230 which is similar to that of FIG. 1 but having concave top and flat bottom surfaces. Other combinations might also be used.

In alternative forms of the invention, still other shapes than full cylinders may be used. For example, it is not required that the full 360° (about axis 10) pad be used if partial disc replacement is undertaken. For angular segment type discs, the cylindrical form may subtend any angle between zero and 360 degrees about axis 10. It is however important that the matrix have characteristics so that when implanted, at least the top and bottom surfaces substantially assume the shape or contour of a natural intervertebral disc.

The various embodiments of the invention may have certain densities of collagen fibers and dispersions of GAG molecules and cross-links that permit accommodation of differing stress levels, rates of ingrowth, and resiliency. Differing densities may be obtained <u>in vivo</u> where a device having uniform density is implanted, and body loading causes non-uniform compression of the device. Alternatively, the prosthetic disc may be initially configured with non-uniform construction of a type so that the <u>in vivo</u> configuration provides the desired spatial densities and dispersions necessary for the desired function.

The prosthetic intervertebral disc may be fabricated

of any biocompatible, bioresorbable fibers such as a natural material, an analog thereof or a synthetic material. The fibers are preferably polymeric in structure so that they can provide mechanical strength, protection, and lubrication while encouraging tissue ingrowth. Such polymeric fibers include, for example, collagen, reticulin, elastin, cellulose, and biosynthetic analogs thereof. These fibers may be ordered in substantially circumferentially-extending or substantially radially-extending orientations, with the density of fibers being substantially uniform throughout the matrix. Alternatively, the matrix fibers may be unordered. In either the ordered or unordered configuration, the density of the fibers may be non-uniform. In the non-uniform configuration, relatively high densities of fibers may be established at anticipated points of high stress.

In an alternative aspect of the invention, the intrafibrillary (i.e., the space within the fiber) and interfibrillary (the space between the fibers) space is relatively high, a condition which promotes ingrowth of regenerated disc tissue. For example, the density of the intervertebral disc may be in the range of 0.07-0.5 g/cm^3 Alternatively, the intrafibrillary and interfibrillary space may be relatively low, a condition which provides superior cushioning, lubrication, and mechanical support for the intervertebral space, and which retards tissue and cell ingrowth, thereby diminishing the rate of scaffold resorption.

The temporary stability of the shape of the structure when in vivo, and the rate of disc resorption, are both attributed to the effective cross-link formation between at least one portion of the fibers. The cross-linking reagents used with the above-noted fiber materials may be any biocompatible, bifunctional reagents which interacts with amino, carboxyl, or hydroxyl groups on a single fiber forming intramolecular cross-links, or on multiple fibers or on the fibers and the GAGs, resulting in covalent bond formation between adjacent molecules (intermolecular cross-links). Useful cross-linking reagents include aldehydes, hexamethylene diisocyanate, bisimidates, polyglycerol polyglycidyl ether, acyl azide, and carbodiimides.

The cross-linked device maintains a sufficient degree of hydrophilicity and elasticity which simulates the properties of the natural intervertebral disc, i.e., ability to sustain mechanical stress and to protect and lubricate articular surfaces. In addition, the structure provides an ideal environment for cell infiltration and extracellular matrix synthesis and deposition, resulting in regeneration of natural disc tissue.

GAGs may be dispersed throughout the fibers. Alternatively, they may act as intermolecular cross-links between fibers. These GAGs typically include at least one of the group of molecules consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate, dermatan sulfate, heparan sulfate, heparin, and hyaluronic acid. The dispersion of GAG cross-links is preferably uniform, but may be more concentrated at anticipated points of high stress, typically at the peripheral region 14, and less concentrated in the central region 12 (FIG. 2). In such configurations, the GAG concentration may be in the range of about 0-25% in the distal region 14, and in the range of about 0-10% in the central region 12. However, when uniform, the dispersion of GAGs throughout the prosthetic intervertebral disc may be, for example, in the range of about 1-15%.

Intermolecular cross-links can also be established through a dehydrothermal process (heat and vacuum) which results in peptide bond formation between an epsilon amino group of lysine or hydroxylysine and a carboxyl group of aspartic or glutamic acid.

The cross-linked disc has a relatively high thermal stability at between about 55-85°C, and preferably at between about 65-75°C for sufficient in vivo stability. This may be achieved through manipulation of the cross-linking conditions, including reagent concentration, temperature, pH, and time (see EXAMPLE 1).

In a one embodiment the prosthetic intervertebral disc is constructed mainly of Type I collagen fibers without GAG cross-links. Type I collagen fibers may be obtained from the Achilles tendons of animals. However, the fibers may also be obtained from animal skin or from the skin or tendon of humans. The tissues are treated with a series of mechanical and chemical means to either totally remove the non-collagenous materials or reduce them to a minimal level. In the preferred processing steps, the tendon or skin is mechanically disintegrated into fine pieces useful for further processing. The disintegration may be achieved by grinding the tissue at liquid nitrogen temperature, or by cutting the tissue into small pieces with a sharp knife. In certain applications, the tendons are mechanically disintegrated along the fiber direction in order to maintain the length of the fibers for mechanical strength.

Salt extraction of tendon at neutral pH removes a small portion of the collagen molecules that are newly synthesized and have not yet been incorporated into the stable fibrils. Salt also removes some glycoproteins and proteoglycans that are associated with collagen through electrostatic interactions. Other salts such as KCl can be used as a substitute for NaCl.

Lipids that are associated with the cell membranes or collagenous matrices may be removed by first extracting with detergents such as Triton X-100 (Sigma Chemical Co., St. Louis, Missouri), followed by extracting with ether-ethanol mixtures. The concentration of Triton X-100 is usually about 2-4%, but is preferably about 3%. The preferred mixture of ether-ethanol is usually at about a 1:1 ratio (v/v). The period of extraction is usually from 8 hours to 96 hours, and is preferably from about 24 to 48 hours.

Further extraction may be accomplished by matrix swelling conducted at two extreme pHs. Both acidic and basic swelling weakens the non-covalent intermolecular interactions, thus facilitating the release of non-covalently attached glycoproteins, GAGs, and other non-collagenous molecules through the open pores of the collagenous matrices.

The swelling of the collagenous matrix at alkaline pH is performed by treating the collagen at high pH with $Ca(OH)_2$, NaOH, or the like, for a period of about 8-96 hours. Alkali extraction in the presence of triple-helical stabilizing salts such as $(CH_3)NCl$ or NH_3SO_4 reduces the potential risk of denaturation of the collagen. Alkali treatment dissociates the non-cross-linked glycoproteins and GAGs from the collagen matrices. The alkali also removes the residual lipids through saponification.

Acid swelling may be conducted at a low pH in the presence of acetic acid, HCl, or similar acids. Like the alkali treatment, the swelling removes non-cross-linked glycoproteins and GAGs.

The non-triple helical portions of the molecule (telopeptides) are involved in intermolecular cross-linking formation. They are weak antigens and are susceptible to attack by proteases such as pepsin and trypsin. Prolonged digestion with such proteases dissociates the fibrils (fibers) into individual molecules. However, if the digestion process is properly controlled such that maximal telopeptides are removed without complete dissociation, the immunogenic properties of the fibrils can be reduced to a minimal level without compromising the mechanical strength. For example, to isolate molecular collagen, the digestion of skin or tendon with pepsin is usually conducted at an enzyme:collagen ratio of about 1:10 for about 24-96 hours at below room temperature. In comparison, fibrils may be obtained by limited pepsin digestion achieved at a ratio of about 1:100 (enzyme:collagen) for about 24-96 hours at 4°C.

Collagen fibers obtained according to this methodology are then used to fabricate the prosthetic intervertebral disc of the present invention. However, it must be appreciated that collagen obtained from other sources, such as biosynthetically-produced collagen or analogs thereof, may also be used in the construction of the prosthetic intervertebral disc.

One method of fabrication includes molding the collagen fibers into a predetermined shape using, for example, the mold forms described below in conjunction with FIGs. 6 and 7. The fibers may be placed randomly in the mold, or may be oriented in specific directions to achieve a intervertebral disc having specific structure characteristics. Other components such as GAGs which may participate in the cross-linking reaction, can be mixed in with the fibers in a random or non-random fashion before the structure is subjected to various cross-linking procedures including chemical methods and/or dehydrothermal methods.

By following the processes described in the examples set forth hereinbelow, a prosthetic intervertebral disc of the form shown in FIGs. 2 or 3 may be constructed having the characteristics listed below in TABLE 1.

TABLE 1

Physical Characteristics
height A = 5 - 12 mm
radius C = 10 - 25 mm
density = 0.07 - 0.5 g/cm^3
intra- and interfibrillary space = 2 - 25 cm^3/g matrix
Constituents
fiber content = 75 - 100%
glycosaminoglycan content = 0 - 25%

The prosthetic discs were evaluated in vivo and in vitro to determine ability to function physically, or to serve as a regeneration template for the fibrochondrocytes expected to serve as precursor cells for the subsequent fibrocartilaginous matrix. These studies demonstrate that the prosthetic disc allows for, and induces fibrochondrocyte infiltration and disc regeneration through the prosthetic material.

The following non-limiting examples describe methods of fabrication and in vivo use of the prosthetic intervertebral disc of the present invention.

EXAMPLE 1

Mold Fabrication

A mold useful for fabricating the prosthetic intervertebral disc is made of implantable stainless steel or biocompatible plastics such as polypropylene, delrin, or combination of these materials. Exemplary molds 100 are composed of three pieces 102, 104, and 106 as shown in FIGs. 6 and 7.

By way of example for the disc-shaped intervertebral disc illustrated in FIGs. 5A and 5B, the mold of FIG. 6 is used. Piece 102 is disc-like and has a diameter substantially equal to that of the desired intervertebral disc. Piece 102 is perforated to allow liquid to pass through under pressure. The inner surface 103 of piece 102 has the desired shape of one side of the intervertebral disc-to-be-formed.

Piece 104 is a hollow cylinder which has the same inner dimension as piece 102. Piece 106 is a cylindrical piston which has an outer diameter slightly less than the inner diameter of piece 104 The "top", or crown, surface 108 of piston 106 has the desired shape of one side of the intervertebral disc-to-be-formed.

For an intervertebral disc having concave top and flat bottom surfaces, the mold of FIG. 7 is used where pieces 102 and 104 are the same as pieces 102 and 104 in FIG. 6, and piece 106 now has a domed surface 108.

During fabrication of the prosthetic disc 230, mold

piece 102 is first assembled within piece 104, as shown in FIG. 6. The constituent fibers (in a fluid) are placed against the surface 103 of piece 102. The crown surface 108 of piston 306 is then driven toward surface 103 along a compression axis until the fibers are compressed, the fluid is driven out through piece 102, and the desired axial dimension of the compressed fiber array is attained. The mold is then frozen in preparation for cross-linking.

EXAMPLE 2

Preparation of Purified Type I Collagen

Bovine, porcine, or sheep Achilles tendon is obtained from USDA-approved slaughter houses. The preferred age of the animals is between 12 - 18 months. The tissue is kept cold during the purification process except where specified to minimize bacteria contamination and tissue degradation.

The adhering tissues of carefully selected tendons are first scrapped off mechanically. The tendons are then minced or cut into fine pieces and washed in excess quantities (about 10 volumes) of cold water to remove residual blood proteins and water soluble materials.

The washed tendons are extracted in ten volumes of 5% NaCl, 0.01 M Tris, pH 7.4, for 24 (+/-4) hours to remove salt soluble materials. The salt-extracted tendons are repeatedly washed in about 10 volumes of water to remove the salt.

To extract lipid, the material is extracted in 3% Triton X-100 for 24 (+/- 2) hours. The detergent is removed by extensive washing with water. The material is then extracted in 3-4 volumes of ether-ethanol (1:1 vol/vol) for 24 (+/- 2) hours to further minimize the lipid content. The lipid extracted material is extensively washed in water to remove the ether and ethanol.

The material is then subjected to two extreme pH extractions to remove non-collagenous materials. Alkaline extraction is conducted with 3-4 volumes of 0.2 M NaOH at pH 12.5 - 13.5 at room temperature in the presence of 1.0 M $(CH_3)NCl$ for 24 (+/- 2) hours with mild agitation.

Following alkaline extraction, the pH is neutralized with HCl, and the material is washed with water. The pH is then adjusted to 2.5 - 3.0 by adding concentrated acetic acid to a final concentration of 0.5 M. The acid extraction is continued for 24 (+/- 2) hours with agitation.

The acid swollen tendon is then subjected to a limited proteolytic digestion with pepsin (enzyme:collagen = 1:100) for 24 (+/-) 2 hours. The pepsin and resulting telopeptides are removed through dialysis.

The swollen fibrillar material is then coacervated by adjusting the pH to its isoionic point with 1 M NaOH or HCl or by adjusting the ionic strength to 0.7 with NaCl. The aggregated collagen fibers are harvested by filtration, and the filtered material extensively washed with cold phosphate buffered saline solution. The highly purified type I collagen may be stored at -20 to -40°C until used.

EXAMPLE 3

Device I Fabrication

A) The collagen content of the highly purified type I collagen fibrils from EXAMPLE 2 is determined either by gravimetric methods or by determining the hydroxyproline content assuming a 13.5% by weight of hydroxyproline in Type I collagen The amount of purified material needed to fabricate a given density of a prosthetic intervertebral disc device is then determined and weighed out.

B) A solution of fibrillar collagen is carefully fit into a mold of desired, specified dimensions (see EXAMPLE I and FIG. 6 for a description of molds). Collagen fibers are laid down in random manner or in an oriented manner. In the oriented manner, circumferential orientation of the fibers is produced by rotation of the piston about its principal axis as the material is compressed in the mold; radial orientation is produced by manual painting of the collagen fibers in a linear, radially directed fashion.

C) The fibers are frozen at -20°C, turned out of the mold, and thawed at room temperature.

D) The fibers are then resuspended in phosphate buffered saline, put back into the mold in the desired orientation(s), and compressed with the piston.

E) The compressed fibers are then refrozen at -20°C and then thawed at room temperature.

F) The resulting structure is cross-linked by soaking in a 0.2% glutaraldehyde solution, pH 7.6, for 24 (+/- 0.5) hours. Each glutaraldehyde-cross-linked prosthetic disc is subsequently rinsed repeatedly in 500 ml of phosphate buffered saline (PBS) solution pH 7.4, for 4, 8, 24 and 48 hours.

G) The rinsed matrix is then lyophilized.

EXAMPLE 4

Device Fabrication

A)-E) (same as EXAMPLE 3)

F) The structure is immersed in an aqueous solution of 0.5 M sodium nitrite, 0.3 M Hcl, and Nacl (OM, 0.34 M, 1.0 M, or 1.34 M) for 3 minutes at 4°C.

EXAMPLE 5

Device II Fabrication

A)-G) (same as in EXAMPLE 3)

H) The lyophilized matrix is subjected to dehydrothermal cross-linking by vacuum and heat. The vacuum is first applied to reduce the residual water content to a minimal level. Some structural water (about 3%) may still be associated with collagen triple-helix as part of the structure stabilizing factor. The heat is increasing in steps to 110°C (+/- 5°), and continually applied at 110°C under vacuum for 24 (+/- 2) hours.

EXAMPLE 6

Device III Fabrication

A) (same as in EXAMPLE 3)

B) The collagen material is dispersed in 0.01 M HCl at pH 2.0 - 2.5. Predetermined amounts of various GAGs are weighed and dissolved in water. For example, for a given density of 0.25 g/cm^2, the collagen content will be 0.244 g, the hyaluronic acid content will be 0.003 g, and the chondroitin sulfate content will be 0.003 g for a 2.5% GAG content. The GAG solution is mixed in with the collagen solution and placed in the mold in the desired orientation as described in EXAMPLE 2.

C)-G) (same as in EXAMPLE 3)

EXAMPLE 7

Device IV Fabrication

A)-C) (same as in EXAMPLE 3)

D) (same as in EXAMPLE 3 except that the fibers laid down are not compressed.

E)-G) (same as in EXAMPLE 3)

EXAMPLE 8

Device V Fabrication

A)-E) (same as in EXAMPLE 3)

F) The molded collagen is cross-linked in 5% polyglycerol polyglycidyl ether in 50% ethanol and 0.1 M Na_2CO_3 at pH 10.0 for 24 (+/- 2) hours. The cross-linked device is rinsed for 4, 8, 24 and 48 hours, each with 500 ml of PBS, pH 7.4.

G) (same as in EXAMPLE 3)

EXAMPLE 9

Device VI Fabrication

A)-E) (same as in EXAMPLE 3)

F) The molded collagen is cross-linked in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (10 mg/g matrix) in 0.9% NaCl, pH 4.7 at room temperature for 24 (+/- 2) hours. The addition of carbodiimide is made every 3 - 4 hours, and the pH is adjusted to 4.7 after each addition of carbodiimide.

G) (same as in EXAMPLE 3)

EXAMPLE 10

Device VII Fabrication

A)-D) (same as in EXAMPLE 2)

E) For attachment purposes, a mesh of absorbable polyglyconate suture material, matched to the size of the mold, is laid in the dispersed collagen such that it protrudes from the structure's periphery to form a skirt which may extend over the vertebral body. This mesh provides both immediate attachment sites and long term fibrous ingrowth.

F)-G) (same as in EXAMPLE 2)

EXAMPLE 11

In vitro Testing

Intervertebral discs are aseptically harvested from mature goats or dogs, trimmed of all adherent tissue, and placed into Gey's balanced saline solution. Each disc is bisected in the coronal plane and 3 mm full-thickness circular defects are made in each half. The defects are filled with a 3 mm diameter plug of one of two prototypes of a complex collagen-based matrix. The discs are placed in six well culture plates containing 6 ml of Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum, sodium ascorbate, and 0.1% penicillin/streptomycin. Cultures are maintained at 37°C in a humidified atmosphere of 10% CO_2/90% air, fed three times per week, and placed in fresh culture wells every week to prevent the formation of explant cell cultures. At intervals of one, four, and six weeks after initiation of culture, three discs from each group are removed, fixed, and evaluated with serial sections and staining. New collagen and glycosaminoglycan formation is evidenced histologically using Alcian Blue and Masson's Trichrome stains.

The results demonstrate increasing cellular migration and invasion over time. There is no apparent toxicity from the material. The depth of cellular penetration into

the scaffold appears to be limited by the density of the prosthetic complex.

EXAMPLE 12

In vivo Testing

The cervical vertebral disc of a mature goat was primarily excised and surgically replaced by a prosthetic disc. The goat returned to full cage activities within a day after surgery. Serial radiographs have documented preservation of the intervertebral joint space.

Claims

1. A prosthetic intervertebral disc (200, 220) comprising a dry, porous volume matrix of biocompatible fibres, said matrix having in vivo an outer surface contour substantially the same as that of a natural intervertebral disc, and said matrix establishing a scaffold adapted for ingrowth of vertebral fibrochondrocytes, characterised in that the prosthetic intervertebral disc is at least partially bioresorbable and comprises a matrix of bioresorbable fibres, the prosthetic intervertebral disc having a density of 0.07-0.5 g/cm^3 and an intrafibrillary and interfibrillary space of 2-25 cm^3/g matrix.

2. The disc of claim 1 wherein said fibers comprise polymers.

3. The disc of claim 1 wherein said fibers are selected from natural fibers, analogs of said natural fibers, synthetic fibers, and mixtures thereof, and for example said natural fibers are selected from collagen, elastin, reticulin, cellulose, analogs thereof, and mixtures thereof.

4. The disc of claim 1 further comprising cross-links between at least a portion of said fibers.

5. The disc of claim 1 further comprising a plurality of glycosaminoglycan molecules interspersed with said fibers.

6. The disc of claim 5, wherein (a) said glycosaminoglycan molecules are selected from the group consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate, dermatan sulfate, heparan sulfate, heparin, hyaluronic acid, and mixtures thereof.

7. The disc of claim 5, wherein at least a portion of said molecules provide cross-links between said fibers.

8. The disc of claim 5, wherein said fibers are present at a concentration of about 75-100% by dry weight, and said glycosaminoglycan molecules are present at a concentration of about 0-25% by dry weight.

9. The disc of claim 4 wherein said cross-links are formed by a chemical cross-linking agent, for example selected from glutaraldehyde, formaldehyde, biocompatible bifunctional aldehydes, carbodiimides, hexamethylene diisocyanate, bis-ionidates, polyglycerol polyglycidyl ether, glyoxal, acyl azide, and mixtures thereof.

10. The disc of claim 9 wherein said cross-linking agent comprises 1-ethyl-3-(3-dimethylaminopropyl).

11. The disc of claim 1 wherein (a) said fibers are oriented in a substantially random fashion throughout said matrix; or (b) said fibers are oriented in a substantially ordered fashion throughout said matrix.

12. The disc of claim 11 wherein (a) said matrix comprises substantially circumferentially extending fibers; or (b) said matrix comprises substantially radially extending fibers.

13. The disc of claim 1 wherein the density of said fibers is substantially uniform throughout said matrix.

14. The disc of claim 1 wherein said fibers are oriented in a substantially ordered fashion in the region adjacent to the peripheral edge of said disc, said orientation being substantially circumferential; and for example wherein said fibers are oriented in a substantially random fashion in the central region of said disc.

15. The disc of claim 5 wherein (a) said glycosaminoglycan molecules are dispersed substantially uniformly throughout said matrix.

16. The disc of claim 1 further comprising a mesh extending from a portion of the outer surface of said matrix, said mesh being resorbable and biocompatible.

17. A method for fabricating a prosthetic intervertebral disc having in vivo an outer surface contour substantially the same as that of a natural intervertebral disc, comprising the steps of:

(a) placing a plurality of biocompatible and bioresorbable fibers into a mold, said mold having a shape that enables disc space function;
(b) subjecting said fibers to a first and a second cycle of freezing and thawing;
(c) contacting said fibers with a chemical cross-linking agent such that said fibers assume the shape of said mould; and
(d) lyophilizing said cross-linked fibers, said prosthetic intervertebral disc thus formed comprising a dry, porous volume matrix having a

density of 0.07-0.5g/cm^3 and an intrafibrillary and interfibrillary space of 2-25cm^3/g matrix, whereby the matrix establishes a bioresorbable scaffold adapted for ingrowth of vertebral fibrochondrocytes.

Patentansprüche

1. Bandscheibenprothese (200,220), die eine trokkene, poröse Volumenmatrix aus biologisch kompatiblen Fasern umfaßt, wobei diese Matrix in vivo eine äußere Oberflächenkontur hat, die im wesentlichen die gleiche wie die einer natürlichen Bandscheibe ist, und die Matrix ein Gerüst bildet, das zum Einwachsen vertebraler Fibrochondrozyten angepaßt ist, dadurch gekennzeichnet, daß die Bandscheibenprothese wenigstens teilweise biologisch resorbierbar ist und eine Matrix aus biologisch resorbierbaren Fasern umfaßt, wobei die Bandscheibenprothese eine Dichte von 0,07 - 0,5 g/cm^3 und einen intrafibrillären und interfibrillären Zwischenraum von 2 - 25 cm^3/g Matrix aufweist.

2. Die Bandscheibe nach Anspruch 1, bei der die Fasern Polymere umfassen.

3. Die Bandscheibe nach Anspruch 1, bei der die Fasern aus natürlichen Fasern, Analogen dieser natürlichen Fasern, synthetischen Fasern und Mischungen derselben ausgewählt sind und die natürlichen Fasern z.B. aus Collagen, Elastin, Reticulin, Cellulose, Analogen derselben und Mischungen derselben ausgewählt sind.

4. Die Bandscheibe nach Anspruch 1, die weiterhin Quervernetzungen zwischen wenigstens einem Teil dieser Fasern umfaßt.

5. Die Bandscheibe nach Anspruch 1, die außerdem eine Vielzahl von Glykosaminoglykan-Molekülen umfaßt, die innerhalb der Fasern und zwischen ihnen verteilt sind.

6. Die Bandscheibe nach Anspruch 5, bei der (a) die Glykosaminoglykan-Moleküle aus der Gruppe ausgewählt sind, die aus Chondroitin-4-sulfat, Chondroitin-6-sulfat, Keratinsulfat, Dermatansulfat, Heparansulfat, Herparin, Hyaluronsäure und Mischungen derselben besteht.

7. Die Bandscheibe nach Anspruch 5, bei der wenigstens ein Teil der Moleküle Quervernetzungen zwischen den Fasern liefert.

8. Die Bandscheibe nach Anspruch 5, bei der die Fasern in einer Konzentration von etwa 75 - 100 % (Trockengewicht) vorhanden sind und die Glykosaminoglykan-Moleküle in einer Konzentration von etwa 0 - 25 % (Trockengewicht) vorhanden sind.

9. Die Bandscheibe nach Anspruch 4, bei der die Quervernetzungen durch ein chemisches Vernetzungsmittel gebildet sind, das z.B. aus Glutaraldehyd, Formaldehyd, biologisch kompatiblen bifunktionellen Aldehyden, Carbodiimiden, Hexamethylendiisocyanat, Bis-ionidaten, Polyglycerolpolyglycidylether, Glyoxal, Acylazid und Mischungen derselben ausgewählt ist.

10. Die Bandscheibe nach Anspruch 9, bei der das Vernetzungsmittel 1-Ethyl-3-(3-dimethylaminopropyl) umfaßt.

11. Die Bandscheibe nach Anspruch 1, bei der (a) die Fasern in einer im wesentlichen statistischen Art durch die Matrix hindurch orientiert sind oder (b) die Fasern in einer im wesentlichen geordneten Weise durch die Matrix hindurch orientiert sind.

12. Die Bandscheibe nach Anspruch 11, bei der (a) die Matrix im wesentlichen sich in Umfangsrichtung erstreckende Fasern umfaßt; oder (b) die Matrix im wesentlichen sich radial erstreckende Fasern umfaßt.

13. Die Bandscheibe nach Anspruch 1, bei der die Dichte der Fasern im wesentlichen gleichmäßig durch die Matrix hindurch ist.

14. Die Bandscheibe nach Anspruch 1, bei der die Fasern in einer im wesentlichen geordneten Weise in dem Gebiet angrenzend an die Umfangskante der Bandscheibe orientiert sind, wobei die Orientierung im wesentlichen in Umfangsrichtung erfolgt; und wobei z.B. diese Fasern in einer im wesentlichen statistischen Weise in dem Zentralbereich der Bandscheibe orientiert sind.

15. Die Bandscheibe nach Anspruch 5, bei der (a) die Glykosaminoglykan-Moleküle im wesentlichen gleichmäßig durch die Matrix hindurch dispergiert sind.

16. Die Bandscheibe nach Anspruch 1, die weiterhin ein Maschengitter umfaßt, das sich von einem Teil der äußeren Oberfläche der Matrix aus erstreckt, wobei das Maschengitter resorbierbar und biologisch kompatibel ist.

17. Ein Verfahren zum Herstellen einer Bandscheibenprothese, die in vivo eine äußere Oberflächenkontur hat, die im wesentlichen die gleiche wie die einer natürlichen Bandscheibe ist, das die Schritte umfaßt, daß:

(a) eine Vielzahl von biologisch kompatiblen und biologisch resorbierbaren Fasern in eine Form gelegt wird, wobei diese Form eine Gestalt aufweist, die eine Bandscheibenab-

standsfunktion ermöglicht;

(b) die Fasern einem ersten und einem zweiten Zyklus des Gefrierens und des Auftauens unterworfen werden;

(c) diese Fasern mit einem chemischen Vernetzungsmittel derart in Kontakt gebracht werden, daß die Fasern die Gestalt dieser Form annehmen; und

(d) die vernetzten Fasern gefriergetrocknet werden, wobei die so gebildete Bandscheibenprothese eine trockene, poröse Volumenmatrix mit einer Dichte von 0,07 - 0,5 g/cm^3 und einem intrafibrillären und interfibrillären Zwischenraum von 2 - 25 cm^3/g Matrix umfaßt, wodurch die Matrix ein biologisch resorbierbares Gerüst bildet, das dem Hineinwachsen von vertebralen Fibrochondrozyten angepaßt ist.

Revendications

1. Disque intervertébral prothétique (200, 220) comprenant un matériau sec poreux en volume de fibres biocompatibles, le matériau ayant in vivo un contour de surface externe pratiquement identique à celui d'un disque intervertébral naturel, et le matériau établissant une ossature adaptée à la croissance interne des fibrochondrocytes vertébraux, caractérisé en ce que le disque intervertébral prothétique est au moins partiellement biorésorbable et comporte un matériau de fibres biorésorbables, le disque intervertébral prothétique ayant une masse volumique de 0,07 à 0,5 g/cm^3 et un espace intrafibrillaire et interfibrillaire compris entre 2 et 25 cm^3/g du matériau.

2. Disque selon la revendication 1, dans lequel les fibres sont des polymères.

3. Disque selon la revendication 1, dans lequel les fibres sont choisies parmi les fibres naturelles, les matières analogues aux fibres naturelles, les fibres synthétiques et leurs mélanges et, par exemple, les fibres naturelles sont choisies parmi le collagène, l'élastine, la réticuline, la cellulose, les matières analogues et leurs mélanges.

4. Disque selon la revendication 1, comprenant en outre des liaisons de réticulation entre une partie au moins des fibres.

5. Disque selon la revendication 1, comprenant en outre plusieurs molécules de glycosaminoglycannes dispersées dans les fibres.

6. Disque selon la revendication 5, dans lequel (a) les molécules de glycosaminoglycannes sont choisies dans le groupe formé par le chondroïtine-4-sulfate, le chondroïtine-6-sulfate, le sulfate de kératine, le sulfate de dermatane, le sulfate d'héparane, l'héparine, l'acide hyaluronique et leurs mélanges.

7. Disque selon la revendication 5, dans lequel une partie au moins des molécules forme des liaisons de réticulation entre les fibres.

8. Disque selon la revendication 5, dans lequel les fibres sont présentes à une concentration d'environ 75 à 100 % en poids à sec, et les molécules de glycosaminoglycannes sont présentes à une concentration d'environ à 25 % en poids à sec.

9. Disque selon la revendication 4, dans lequel les liaisons de réticulation sont formées par un agent chimique de réticulation, choisi par exemple parmi le glutaraldéhyde, le formaldéhyde, les aldéhydes bifonctionnels biocompatibles, les carbodiimides, l'hexaméthylènediisocyanate, les bis-ionidates, l'éther polyglycidylique de polyglycérol, le glyoxal, l'azothydrure d'acyle et leurs mélanges.

10. Disque selon la revendication 9, dans lequel l'agent de réticulation contient du 1-éthyl-3-(3-diméthylaminopropyle).

11. Disque selon la revendication 1, dans lequel (a) les fibres sont orientées de manière pratiquement aléatoire dans le matériau, ou (b) les fibres sont orientées de manière pratiquement ordonnée dans le matériau.

12. Disque selon la revendication 11, dans lequel (a) le matériau comprend pratiquement des fibres placées circonférentiellement, ou (b) le matériau comprend les fibres disposées pratiquement en direction radiale.

13. Disque selon la revendication 1, dans lequel la masse volumique des fibres est pratiquement uniforme dans tout le matériau.

14. Disque selon la revendication 1, dans lequel des fibres sont orientées de manière pratiquement ordonnée dans la région adjacente au bord périphérique du disque, l'orientation étant pratiquement circonférentielle et, par exemple, les fibres sont orientées de manière pratiquement aléatoire dans la région centrale du disque.

15. Disque selon la revendication 5, dans lequel (a) les molécules de glycosaminoglycannes sont dispersées de manière pratiquement uniforme dans tout le matériau.

16. Disque selon la revendication 1, comprenant en outre une grille partant d'une partie de la surface

externe du matériau, la grille étant résorbable et biocompatible.

17. Procédé de fabrication d'un disque intervertébral prothétique ayant in vivo un contour de surface externe pratiquement identique à celui d'un disque intervertébral naturel, comprenant les étapes suivantes :

(a) la disposition de plusieurs fibres biocompatibles et biorésorbables dans un moule, le moule ayant une configuration qui permet une fonction d'espacement de disque,
(b) l'application aux fibres d'un premier et d'un second cycle de congélation-dégel,
(c) la mise en contact des libres avec un agent chimique de réticulation tel que les fibres prennent la configuration du moule, et
(d) la lyophilisation des fibres réticulées, le disque intervertébral prothétique ainsi formé comprenant un matériau sec et poreux en volume ayant une masse volumique comprise entre 0,07 et 0,5 g/cm^3 et un espace intrafibrillaire et interfibrillaire de 2 à 25 cm^3/g du matériau, et le matériau établit une ossature biorésorbable destinée à permettre la croissance interne des fibrochondrocytes vertébraux.

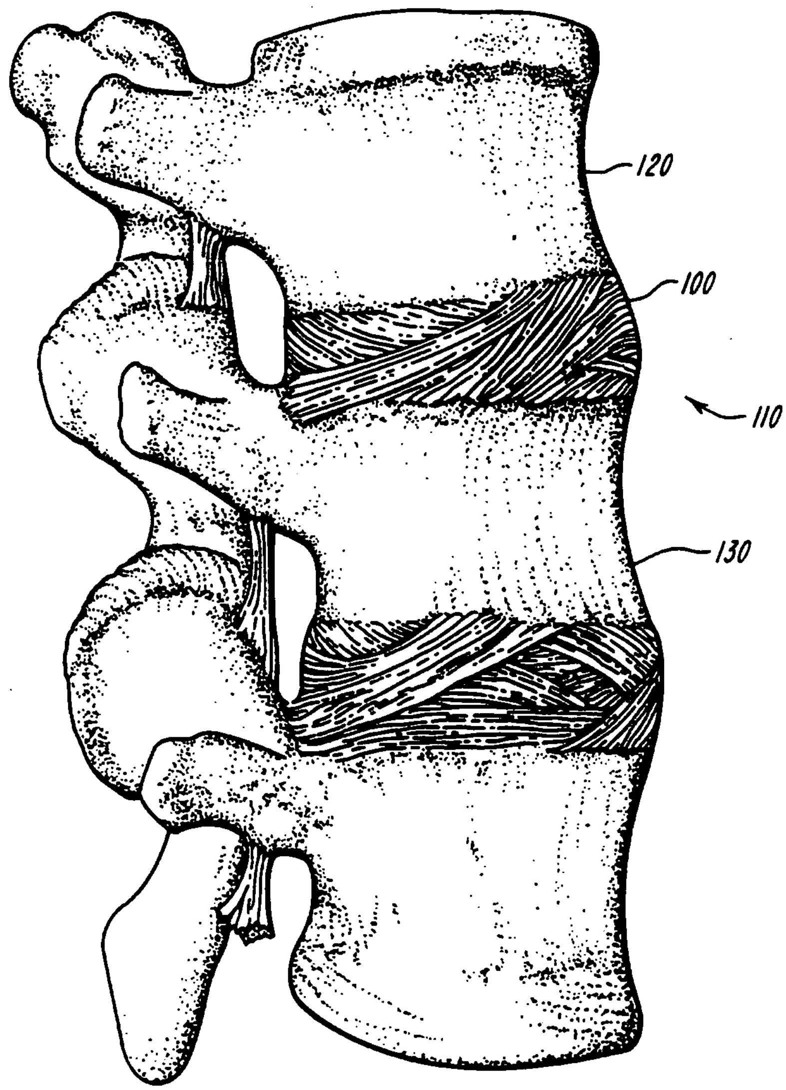

FIG. 1

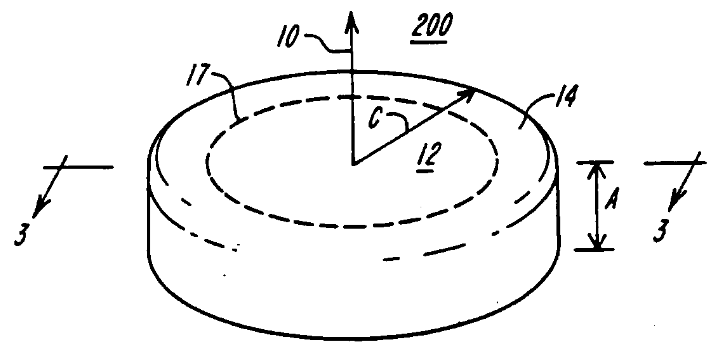

FIG. 2

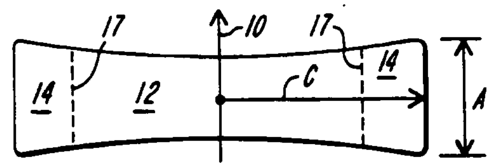

FIG. 3

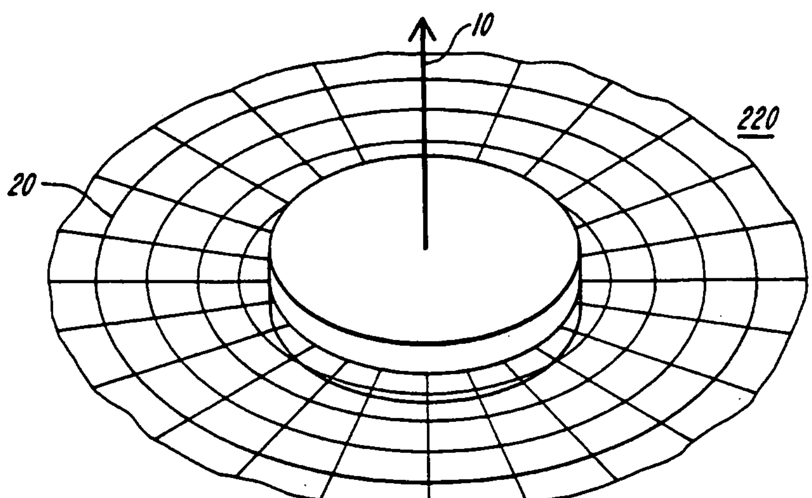

FIG. 4

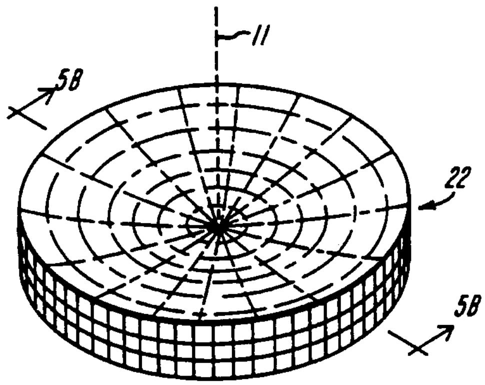

FIG. 5A

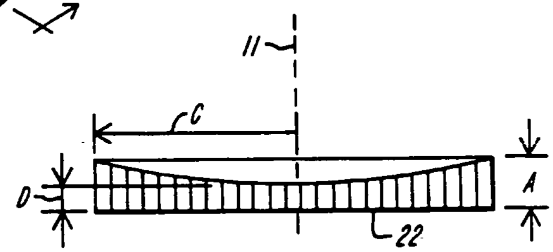

FIG. 5B

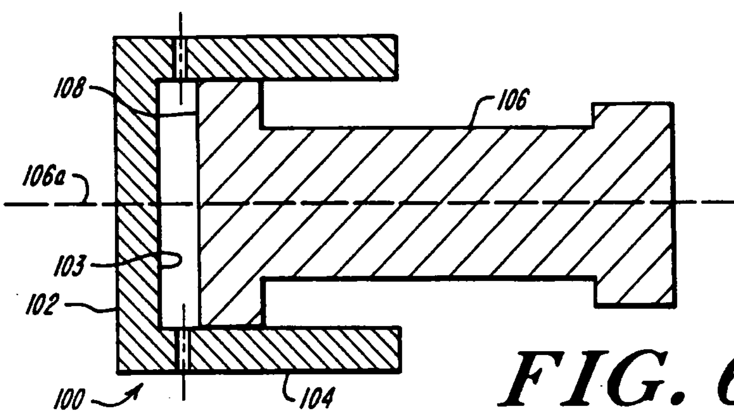

FIG. 6

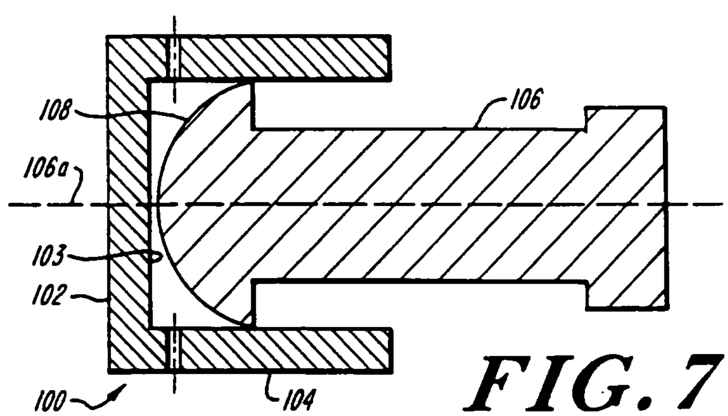

FIG. 7